Paul Fornes,[1] *M.D., Ph.D.; Sylvie Ratel,*[1] *M.D.; and Dominique Lecomte,*[1] *M.D.*

Pathology of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia—An Autopsy Study of 20 Forensic Cases*

REFERENCE: Fornes P, Ratel S, Lecomte D. Pathology of arrhythmogenic right ventricular cardiomyopathy/dysplasia—An autopsy study of 20 forensic cases. J Forensic Sci 1998;43(4): 777–783.

ABSTRACT: Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVC) is characterized histologically by massive infiltration of the right ventricular wall by fat tissue, with surviving strands of cardiomyocytes bordered by or embedded in fibrosis. ARVC has been recognized as a cause of sudden death, especially in the young.

The purpose of our autopsy study was to examine the clinical characteristics and the pathological patterns in the hearts of 20 people who died suddenly of ARVC. In view of our findings and the literature, we discussed the possible causes and pathogenesis of ARVC, as well as the mechanisms by which sudden death occurs in this disease.

During the 7-year study period, 20 hearts from 9 men and 11 women fulfilled the criteria for ARVC. The mean age was 41 years (range, 17 to 80). The disease was unknown prior to death in all cases. Fourteen persons died at rest, and six on effort. In 9 of the 20 cases, the trigger of sudden death was an acute emotional stress, sometimes associated with a moderate physical activity. The mean heart weight was 380 g (range, 280 to 520). Both ventricles were involved in 40% of the cases. Inflammatory infiltrates consisting of lymphocytes were present in 60% of the cases, but myocyte necrosis was found in only one case.

ARVC is more likely to result from a degenerative process than a congenital disorder. Genetic factors, viral or autoimmune inflammation or both, and apoptosis are also involved in the degenerative disorder.

KEYWORDS: forensic sciences, sudden death, right ventricular dysplasia; forensic pathology, autopsy

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia, is a heart muscle disease characterized by fibrofatty infiltration of the right ventricle (1–11). The etiology and natural history of this condition are still unclear (1,12–20). ARVC is now well recognized as a cause of sudden death. The victims are mostly young people, and sudden death is often the first manifestation of the disease (1–3,8,9,11,21). Therefore, such an unexpected death occurring in a young, otherwise healthy, person is likely to be viewed by the law as a suspicious death and requires a medicolegal autopsy. In this context, it is not uncommon for a medical examiner to encounter such a death and to face its legal implications.

The purpose of our autopsy study was to examine the clinical characteristics and the pathological patterns in the hearts of 20 people who died suddenly of ARVC. In view of our findings and the literature, we discussed the possible causes and pathogenesis of ARVC, as well as the mechanisms by which sudden death occurs in this disease.

Methods

Definitions

Sudden Death—In the present study, sudden death has been defined as a natural, unexpected death occurring within one hour after the onset of symptoms (1,21). Included in the study were only those cases in which the death was witnessed or there was sufficient circumstantial evidence of sudden death. Thus, the activity in which the decedent was engaged when he died, the position or posture of the body, and the possible contusions received by the body on falling unconscious were investigated in order to determine whether the death had been sudden.

Arrhythmogenic Right Ventricular Cardiomyopathy—The pathological diagnosis of ARVC was assessed in the presence of gross or histologic evidence or both of regional or diffuse transmural fibrofatty infiltration of the right ventricular free wall reaching the endocardium in the absence of valve, coronary, and pericardial disease (1). The regions of the right ventricle most frequently involved are the right ventricular inflow, apex, and infundibulum, known as the triangle of dysplasia. On the basis of this definition, some authors distinguished two different patterns (1). In the fibrofatty variety, myocardial loss is replaced by both fibrous and fatty tissue, whereas in the fatty variety myocardial loss is replaced exclusively by fatty tissue with or without tiny interstitial fibrosis (1). However, not all authors are in agreement with this definition (9,15). Like these authors we consider that the presence of fibrous tissue is necessary for the diagnosis of ARVC. Cases in which fatty tissue is limited to the subepicardium or only infiltrate the outer third of the myocardium should be excluded. Figures 1 and 2 show normal ventricular wall and typical pattem of ARVC, respectively. Figure 3 shows gross massive transmural infiltration of the right ventricular wall, but histologically, strands of cardiomyocytes were found in fat tissue without fibrosis. Such a case was excluded from our study.

[1] Institute of Forensic Medicine of Paris and Department of Forensic Sciences, College of Medicine Cochin Port-Royal, University of Paris, Paris, France.

* Presented at the 49th Annual Meeting, American Academy of Forensic Sciences, New York, NY, February 1997.

Received 30 July 1997; and in revised form 3 Dec. 1997; accepted 3 Dec. 1997.

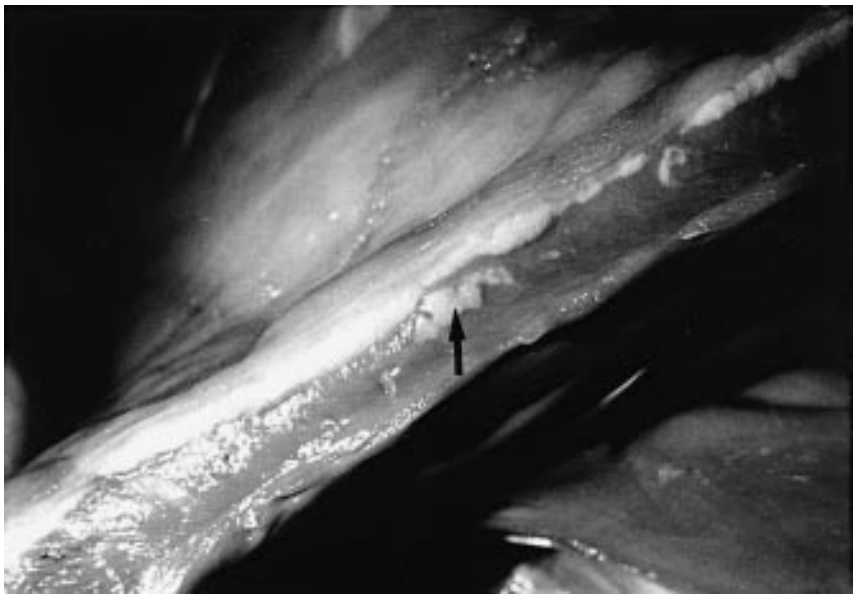

FIG. 1—*Gross view of a heart specimen showing normal pattern of the right ventricular free wall. The fat tissue is limited to the subepicardium and slightly infiltrates the myocardium (arrow).*

Study Population

In the present series all victims of sudden death fulfilling the above-defined pathological criteria for ARVC, and autopsied between 1990 and 1996 have been included.

Pathological Study

Complete autopsies and histologic examination of all organs were systematically performed. Toxicological analyses were performed when a toxic death could not be ruled out on the basis of the autopsy findings and the circumstances of death. The hearts were weighed fresh without removing the epicardial adipose tissue. They were thoroughly examined for coronary artery and valve diseases. Then, at least 7 specimens were taken from the myocardium. Histologic sections were stained with hematoxylin and eosin, and Masson's trichrome for collagen network.

Results

During the 7-year study period, 20 hearts from 9 men and 11 women fulfilled the criteria for ARVC. The mean age of these 20 subjects was 41 years. The 9 men ranged in age from 17 to 42, mean age 34 years, and the 11 women from 24 to 80 years, mean age 48.5 years.

A heart disease had been previously diagnosed in one man aged 24 and in a woman aged 70, but the cause of the diseases had not been determined. The father of a female victim aged 27 died of a heart disease of unknown origin.

The mode of death was sudden in all cases. No person was reported to have experienced symptoms at the onset of death. Fourteen persons died at rest, and six on effort. Three men, aged 17, 21, and 25, died during a sporting activity (basketball, football, and gymnastic exercises); one of them died during the recovery phase after the football training session. Two women, aged 60 and 80 died during muggings. Two men, aged 24 and 28, and one 26-year-old woman died during sexual intercourse under stressful conditions. A 36-year-old male victim was hit by a car but was only slightly injured. He collapsed in the hospital shortly after the accident. Two women, aged 56 and 33, died in the hospital during X-ray examination. A 27-year-old woman dropped dead during a witnessed argument on the phone. Two deaths occurred in restrooms, one death in a railway station. The five remaining victims were found in their home. One died during sleep, 2 were watching television, 2 died during breakfast. In 9 out of 20 cases the trigger of sudden death was an acute emotional stress.

The mean heart weight was 380 g (range, 280 to 520), 360 g in males (range, 320 to 520) and 315 g in females (range, 280 to 410). Sixteen hearts of the 20 were normal in weight. Right ventricular thickness (including fat and muscle) was considered normal in all cases. The right ventricular cavity was enlarged in one case involving also the left ventricle. Fatty infiltration involved the outer half of the right ventricular free wall in 27% of the cases, the two outer third in 28%, and was transmural in 45% of the cases. Even in the diffuse pattern residual myocytes were scattered within the fibrofatty tissue. The subendocardial muscular trabeculae appeared to be mostly spared. The left ventricle was involved in 40% of the cases. Inflammatory infiltrates consisting of lymphocytes were present in 60% of the cases, but myocyte necrosis was found in only one case (Fig. 4).

Discussion

Arrhythmogenic right ventricular dysplasia was the name given in 1977 to a new form of cardiomyopathy that showed fatty infiltration of the right ventricle (22). Originally, this disease, considered to be due to an abnormality in the development of the right ventricular musculature, was classified as a variant of Uhl's anomaly (23). In 1952 Uhl described a congenital malformation of the heart in which the right ventricle was paper thin and in some places totally devoid of muscle fibers, an appearance similar to the parchment heart reported by Osler (24). Although the etiology and natural history of ARVC remain obscure, Uhl's anomaly and ARVC are now considered two separate clinical entities because of their different clinical and pathological patterns (1,4,5,13). Firstly, ARVC appears in adolescence or young adulthood, not at birth or in the infancy (1). In this regard, the acquired nature of the disease is also corroborated by the wide age range of the victims found in

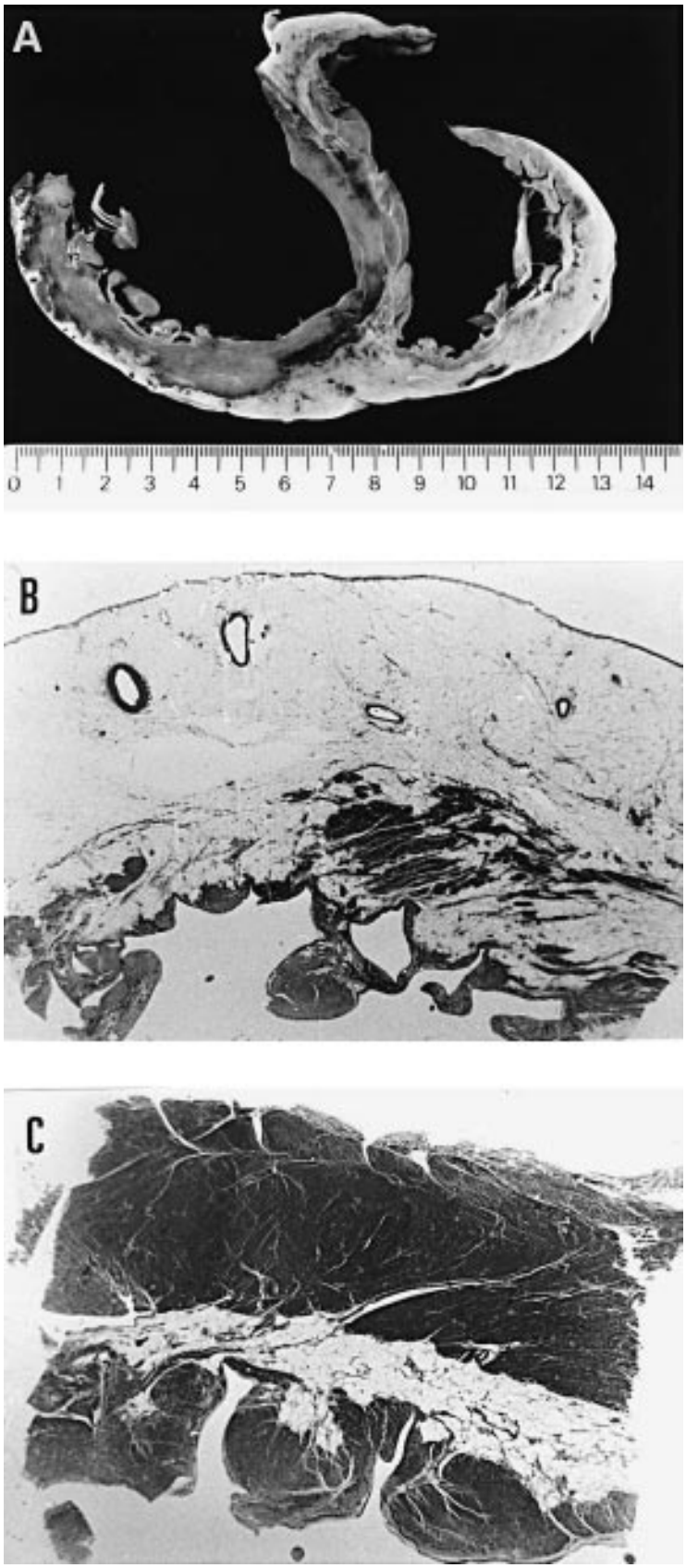

FIG. 2—*Panel A: Cross section of a heart specimen with ARVC from a 17-year-old man who died during a basketball match. Both ventricles are involved. Panel B: Corresponding panoramic histological view of the right ventricular free wall showing transmural fibrofatty replacement. Original magnification: ×2.5; Stain: Masson's trichrome. Panel C: Corresponding panoramic histological view of the septal wall showing mediomural fibrofatty infiltration. Original magnification: ×2.5; Stain: Masson's trichrome.*

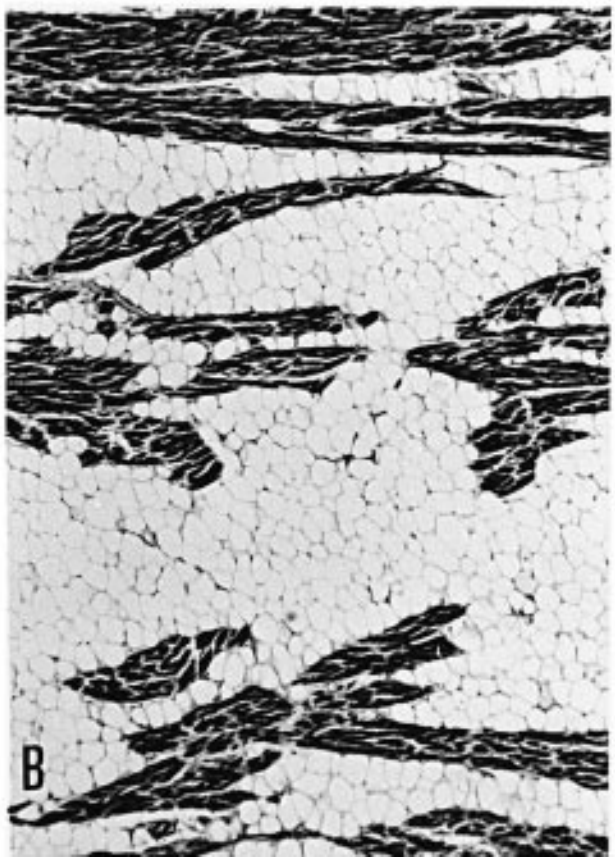

FIG. 3—*Panel A: Cross section of a heart specimen with important fatty infiltration, in a 96-year-old woman who died of carbon monoxide intoxication in a fire. Panel B: Strands of cardiomyocytes are embedded in adipose tissue, but there was no fibrosis. Original magnification: ×100; stain: Masson's trichrome.*

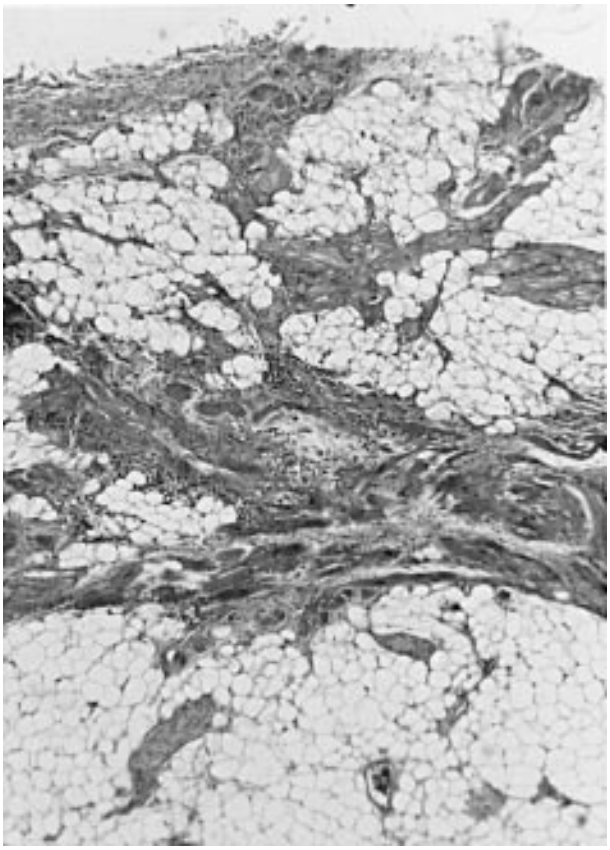

FIG. 4—*Histologic view of the right ventricle showing fibrofatty infiltration and inflammatory infiltrates. Original magnification: ×100; stain: hematoxylin-eosin-saffron.*

our series as well as in others (1,24). Secondly, in ARVC the free wall of the right ventricle is not parchmentlike as it is in Uhl's anomaly, and the distance between the epicardium and the endocardium is normal or slightly decreased (1). Finally, there is histologic evidence of progressive loss of right ventricular myocardium, with foci of inflammation, degeneration and necrosis (1). For these reasons, the term arrhythmogenic right ventricular cardiomyopathy is better than arrhythmogenic right ventricular dysplasia, which means developmental malformation.

In the degenerative theory, as opposed to the disontogenic theory, the loss of the myocardium is considered to be the consequence of progressive myocyte death due to some metabolic or ultrastructural defect (1). Familial occurrence suggests a genetic disease with autosomal dominant transmission and variable expression and penetrance (18,19,25). The finding of a gene defect localized on chromosome 14q23-q24 favors a genetically determined atrophy (19).

In the inflammatory theory, the fibrofatty replacement is viewed as a healing process in the setting of chronic myocarditis (1,14,20). The disappearance of the right ventricular myocardium might be the consequence of an inflammatory necrotic injury followed by fibrofatty repair. This is not in contrast to a familial occurrence because a genetic predisposition to viral infection eliciting immune reaction cannot be excluded (1,14). Genetic factors may play a role not only in susceptibility to infections but also in the site of cardiac involvement, namely, the myoepicardium of the right ventricle. However, whether the inflammation is a primary event or secondary to the spontaneous cell death is an unanswered question (1,14).

Finally, it was recently advanced that myocardial cell death in ARVC might represent a programmed death known as apoptosis (1,15,26).

Regarding pathological patterns of ARVC, the relatively high prevalence of left ventricular involvement found in our series as well as in others suggest that this disease should no longer be considered as limited to the right ventricle (1,27–31). However, in contrast to other dilated cardiomyopathies, ARVC is rarely a cause of cardiac failure but much more frequently responsible for sudden death (1,31,32).

Previous studies on ARVC have often focused on sudden death among young people and competitive athletes and have found a physical strenuous activity to be a major trigger of sudden death in ARVC (1). Our data based on medicolegal cases show that not only a physical stress may be involved, but also an acute psychological stress. We found an acute emotional stress to be more frequently involved than a physical stress as a trigger of sudden death. This finding is probably partly due to the specificity of the medicolegal population. During both physical and emotional stress, the electric instability leading to the onset of the lethal arrhythmia could be modulated by the influence of the autonomic nervous system and the release of catecholamines.

Atrioventricular conduction disturbances are rarely a cause of sudden death in patients with ARVC (33). Atrioventricular conduction disturbance is a well-recognized cause of sudden death in elderly patients, but is rare in young patients who do not have congenital heart block. However, during strenuous exercise the increase in venous return could dilate the right atrium and ventricle and stretch the atrioventricular conduction system, in which the His bundle is the most fragile structure (33). Mechanical stretch of the His bundle or the bundle branches could lead to atrioventricular block and could also lead to other arrhythmias. However, it is unlikely that atrioventricular block is responsible for sudden death in most cases. Ventricular arrhythmia, including ventricular tachycardia would seem to be a more frequent cause of death in those patients. It has been suggested that strands of surviving fibers form an arrhythmogenic substrate in ARVC, and provide the appropriate conditions necessary to establish a re-entrant pathway (33,34). Another mechanism of ARVC could be related to the stretch of fibers during exercise (33). Because of the increase in venous return, enlargement of the right ventricular myocardium as a result of physical stress might be a mechanism of sudden death in strenuous physical activities, such as a sporting activity. Of note, sudden death occurs sometimes during the recovery phase after effort (33). This is what happened in one of our cases. This could be due to the effect of heart rate on premature ventricular complexes (33). The increase in heart rate during physical stress may decrease the frequency of premature ventricular complexes. The reversed phenomenon could occur during the recovery phase increasing the risk of ventricular arrhythmia. This is due to the abrupt suppression of the sympathetic tone and a major increase in the vagal tone during the recovery phase after effort. Moreover, there is an abrupt decrease in right ventricular filling that could lead to hypotension by suppression of the pump effect produced by muscular contractions (33).

Although sudden death is frequently the first manifestation of ARVC, the disease is sometimes diagnosed in symptomatic and even in asymtomatic patients (1). Therefore, questions about the screening and disqualification of athletes have generated considerable debate and stimulated concern among experts in sports medicine and the legal profession. Recently, major and minor criteria for a positive diagnosis of ARVC have been proposed (9). The diagnosis of ARVC is fulfilled by the presence of two major criteria

TABLE 1—*Criteria for ARVC.**

Major Criteria	Minor Criteria
Structural or Functional Abnormalities	**Structural or Functional Abnormalities**
Severe dilatation and reduction of right ventricular ejection fraction with none (or only mild) left ventricular impairment	Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle
Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging)	Regional right ventricular hypokinesis
Severe segmental dilatation of the right ventricle	Mild segmental dilatation of the right ventricle
Tissue Characterization of Walls	**Arrhythmias**
Massive infiltration of right ventricular external layers by fat, with presence of surviving strands of cardiomyocytes bordered by or embedded in fibrosis	Left bundle branch block VT (sustained or non sustained on ECG, or Holter)
Repolarization Abnormalities	Frequent PVCs (1000/24 hours on Holter)
T wave inversion in V1 to V3 or beyond	**Conduction Abnormalities**
Conduction Abnormalities	Inverted T waves in right precordial leads (V2–3 in people >12 years, in the absence of RBB
QRS complex duration >110 msec in V1 or V2 or V3	Late potentials in signal averaged ECG
RBBB with QRS duration in V1, V2 or V3 50 msec greater than in V6	**Family History**
Epsilon Wave	Familial history of premature sudden death (<35 years) due to suspected ARVC
Family History	Familial history (clinical diagnosis based on present criteria)
Familial disease confirmed at necropsy or surgery	

** Criteria for diagnosis of ARVC established by the Arrhythmogenic Right Ventricular Dysplasia Registry of the United States. Standardized diagnostic criteria are based on the presence of major and minor criteria encompassing structural, histological, echocardiographic, arrhythmic and genetic factors. The diagnosis of ARVC is fulfilled by the presence of 2 major criteria or 1 major criterion plus 2 minor criteria or 4 minor criteria.*

or one major criterion plus two minor criteria or four minor criteria. Table 1 lists these criteria.

Conclusion

ARVC is a relatively rare, but probably an underestimated cause of sudden death. Our data confirm that sudden death is often the first manifestation of this disease. An acute emotional stress is frequently involved. Recognition of ARVC as a possible cause of sudden death by the medical examiner is important in elucidating medicolegal implications of some sudden deaths. Medicolegal autopsies are also useful to enhance our clinical awareness and diagnostic acumen with regard to this disease, and to identify asymtomatic family members at risk.

References

1. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic right ventricular cardiomyopathy/dysplasia, dystrophy, or myocarditis? Circulation 1996;94:983–91.
2. Berder V, Vauthier M, Mabo P, De Place C, Laurent M, Almange C, et al. Characteristic and outcome in arrhythmogenic right ventricular dysplasia. Am J Cardiol 1995;75:411–4.
3. Corrado D, Thiene G, Nava A, Rossi L, Pennelli N. Sudden death in young competitive athletes: clinicopathologic correlation in 22 cases. Am J Med 1990;89:588–96.
4. Fontaine G, Fontaliran F. Arrhythmogenic right ventricular disease, dysplasia and cardiomyopathy. Eur Heart J 1996;17:1613–4.
5. Fontaine G, Fontaliran F, Rosas Andrade F. et al. The arrhythmogenic right ventricle. Dysplasia versus cardiomyopathy. Heart and Vessels 1995;10:227–35.
6. Lobo FV, Heggtveit HA, Butany J, Silver MD, Edwards JE. Right ventricular dysplasia: morphological findings in 13 cases. Can J Cardiol 1992;8:261–8.
7. Marcus FI, Fontaine G, Guiraudon G, Frank R, Laurenceau JL, Malergue S, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384–98.
8. Maron BJ. Right ventricular cardiomyopathy: another cause of sudden death in the young. N Engl J Med 1988;318:178–9.
9. McKenna WJ, Thiene G, Nava A, Fontaliran F, Blomstrom-Lundqvist C, Fontaine G, et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 1994;71:215–8.
10. Siragusa JJ, McDermott WM, Amorosino CS. Right ventricular cardiomyopathy: Another cause of sudden death in the young. N Engl J Med 1988;318:178–80.
11. Thiene G, Nava A, Corrado D, Rossi L, Pennelli N. Right ventricular cardiomyopathy and sudden death in young people. N Engl J Med 1988;318:129–33.
12. Canciani B, Nava A, Toso V, Martini B, Thiene G. A casual spontaneous mutation as possible cause of the familial form of arrhythmogenic right ventricular cardiomyopathy (arrhythmogenic right ventricular dysplasia). Clin Cardiol 1992;15:217–9.
13. Gerlis LM, Schmidt-Ott C, Ho SY, Anderson RH. Dysplastic conditions of the right ventricular myocardium: Uhl's anomaly vs. arrhythmogenic right ventricular dysplasia. Br Heart J 1993;69: 142–50.
14. Hofmann R, Trappe HJ, Klein H, Kemnitz J. Chronic (or healed) myocarditis mimicking right ventricular dysplasia. Eur Heart J 1993;14:717–20.
15. Mallat Z, Tedgui A, Fontaliran F, Frank R, Durigon M, Fontaine G. Evidence of apoptosis in arrhythmogenic right ventricular dysplasia. N Engl J Med 1996;335:1190–8.
16. Manyari DE, Klein GJ, Gulamhusein S, Boughner D, Guiraudon GM, Wyse G, et al. Arrhythmogenic right ventricular dysplasia: a generalized cardiomyopathy? Circulation 1983;68:251–7.
17. Nava A, Thiene G, Canciani B, Scognamiglio R, Daliento L, Buja GF, et al. Familial occurrence of right ventricular dysplasia: a study involving nine families. J Am Coll Cardiol 1988;12:1222–8.
18. Rakover C, Rossi L, Fontaine G, Sasel B, Markez J, Voncina D. Familial arrhythmogenic right ventricular disease. Am J Cardiol 1986;58:377–8.
19. Rampazzo A, Nava A, Danieli GA, Buja GF, Daliento L, Fasoli G, et al. The gene for arrhythmogenic right ventricular cardiomyopathy maps to chromosome 14q23-q24. Hum Mol Genet 1994;3: 959–62.
20. Thiene G, Corrado D, Nava A, Rossi L, Poletti A, Boffa GM, et al. Right ventricular cardiomyopathy: is there evidence of an inflammatory actiology? Eur Heart J 1991;12:22–5.
21. Furlanello F, Bettini R, Bertoldi A, Vergara G, Visonà L, Durante GB, et al. Arrhythmia patterns in athletes with arrhythmogenic right ventricular dysplasia. Eur Heart J 1989;10:16–9.
22. Fornes P, Lecomte D, Nicolas G. Sudden out-of-hospital coronary death in patients with no previous cardiac history. An analysis of 221 patients studied at autopsy. J Forensic Sci 1993;38: 1084–91.
23. Marcus F, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. Pace 1995;18:1298–314.
24. Uhl HSM. A previously undescribed congenital malformation of the heart: almost total absence of the myocardium of the right ventricle. Bull Johns Hopkins Hosp 1952;91:197–209.
25. Osler WM. The principles and practice of medicine. 6th ed. New York: D'appleton & Co. 1905;820.

26. Daliento L, Turrini P, Nava A, Rizzoli G, Angelini A, Buja GF, et al. Arrhythmogenic right ventricular cardiomyopathy in young versus adult patients: similarities and differences. J Am Coll Cardiol 1995;25:655–64.
27. Nava A, Scognamiglio R, Thiene G, Canciani B, Daliento L, Buja GF, et al. A polymorphic form of familial arrhythmogenic right ventricular dysplasia. Am J Cardiol 1987;59:1405–9.
28. James TN. Normal and abnormal consequences of apoptosis in the human heart: from postnatal morphogenesis to paroxysmal arrhythmias. Circulation 1994;90:556–73.
29. Gallo P, D'Amati G, Pelliccia F. Pathologic evidence of extensive left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy. Hum Pathol 1992;23:948–52.
30. Webb J, Kerr C, Huckell V, Mizgala H, Ricci D. Left ventricular abnormalities in arrhythmogenic right ventricular dysplasia. Am Heart J 1986;58:568–70.
31. Okada E, Okuda K. A case of right ventricular dilated cardiomyopathy. Am J Cardiovasc Pathol 1994;5:1–10.
32. Pinamonti B, Sinagra G, Salvi A, Di Lenarda A, Morgera T, Silvestri F, et al. Left ventricular involvement in right ventricular dysplasia. Am Heart J 1992;123:711–24.
33. Jaoude SA, Leclercq JF, Coumel P. Progressive ECG changes in arrhythmogenic right ventricular disease. Evidence for an evolving disease. Eur Heart J 1996;17:1717–22.
34. William G, Fuster V. Idiopathic dilated cardiomyopathy. N Engl J Med 1994;331:1564–75.
35. Fontaine G, Fontaliran F, Iwa T, Aouate P, Naditch L, Lascault G, et al. Arrhythmogenic right ventricular dysplasia. Definition and mechanism of sudden death in: Akhtar M, Myerburg RJ, Ruskin JN, editors. Sudden cardiac death. Prevalence, mechanisms, and approaches to diagnosis and management. Williams and Wilkins, Malvern, PA, 1994;226–37
36. Turrini P, Angelini A, Buja GF, Nava A, Thiene G. Fibrosis is the main cause of late potentials in arrhythmogenic right ventricular cardiomyopathy. Circulation 1994;90:1–229.

Additional information and reprint requests:
Paul Fornes, M.D., Ph.D.
Department of Pathology (Laboratoire d'Anatomo-pathologie), Hôpital Broussais
96, rue Didot, 75014 Paris, France